Application No.:	10/684,042
Applicant:	Jörn Bullerdiek
Filed:	October 10, 2003
Title:	NUCLEIC ACID SEQUENCES OF HYPERPLASIAS AND TUMORS OF THE THYROID
Art Unit:	1642
Confirmation No.:	3162
Examiner:	Misook Yu
Docket No.:	350935-002 (BL-001/US)

Mail Stop Amendment
Commissioner for Patents
P.O. Box 1450
Alexandria, Virginia 22313-1450

DECLARATION OF DR. JÖRN BULLERDIEK UNDER 37 C.F.R. § 1.132

Dear Sir:

I, Jörn Bullerdiek, hereby declare that:

1. I am one of the inventors of the invention disclosed in the above-identified patent application ("the '042 application"), and, thus, I am familiar with the application and the invention claimed therein.
2. I was awarded a doctorate at the University of Bremen in 1982.
3. I presently hold the position of Head of the Center for Human Genetics at the University of Bremen. A *curriculum vitae* is attached herewith as **Exhibit A**.
4. I have reviewed and understand the Office Action mailed September 8, 2008. I am submitting this declaration to respond to some of the Examiner's comments regarding the utility of using antibodies for the diagnosis and/or treatment of functional disorders of the thyroid and/or hyperplasias of the thyroid and/or thyroid tumors.
5. One of skill in the art would recognize that differential expression of, for example, mRNA associated with SEQ ID NO:12, would lead to the differential expression of translation products related to such mRNA. The concept is referred to as the "central dogma" of biology. The correlation between the differential expression of mRNA leading to the differential expression of protein is the fundamental concept driving the studies described in the '042 application. It is the central dogma of biology, that would be recognized by one of ordinary skill in the art, that would allow one of skill in the art that, because there is a clear demonstration of the differential expression of, for example, SEQ ID NO:12, wherein the differential expression is demonstrated to be a differential expression of mRNA, that there would also be a corresponding differential expression of the protein product.
6. I have attached herewith additional data indicating the differential expression of SEQ ID NO:12. Exhibit B contains tables that demonstrate the over-expression of the mRNA coding for CAT-A (referred to as CAT-12 in said tables and corresponding to SEQ ID NO:12 (the genomic sequence)). Cell lines EFM 19 and MCF7 show a significant

increase of the respective mRNA expression. "Ct" is indicative for the expression level of the mRNA.

7. Exhibit C contains table 4.2.1, which clearly shows that in follicular adenoma as a representative example for a benign thyroid tumor and thyroid disorder, mRNA for *CAT-12* is significantly over-expressed.

8. These additional data, albeit relating to mRNA expression, show that gene expression, whether measured by determining levels of mRNA or by determining levels of protein, are useful for diagnostic purposes. Ultimately, the usefulness of the described findings derive from the detection of gene expression products (including both mRNA and protein). The relationship between mRNA and protein, again- a fundamental biological relationship, would allow one of skill in the art to recognize the usefulness of a diagnostic based on the differential expression of a gene expression products, whether that gene expression product is mRNA or protein.

9. I declare further that all statements made in this Declaration of my own knowledge are true, that all statements made on information and belief are believed to be true, and further, that these statements are made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of any patent that may issue from the present application.

Respectfully submitted,

Jörn Bullerdiek
Date: March 6, 2009

Exhibit A

Jörn Bullerdiek, Curriculum Vitae

Birth date / place	28. April 1955, Bremen, Germany

Academic studies

1974-1979	Biology, University of Bremen, Germany (scholarship holder of the “German National Academic Foundation“)
1979	Graduation as Dipl.-Biol., diploma thesis: "Standardization of culture conditions of human embryonic/fetal cells in long term cell culture“
1982	Graduation as Dr. rer. nat. at the University of Bremen Doctoral thesis: "Amniotic fluid cell culture as a model system for biological and genetic examinations in humans“, doctoral thesis supervisor: Prof. Dr. W. Schloot

Professional activities

1979-1980	**Research assistant at the University of Bremen, assignment: assistance in the laboratory course**
1980	**Scientist (“wissenschaftlicher Mitarbeiter“) at the local health authority (Hauptgesundheitsamt Bremen), responsibility: pre- and postnatal chromosome diagnostics**
1983	**Appointment as scientific councilor (“wissenschaftlicher Rat z.A.“), appointment for life as a civil servant (“Beamter auf Lebenszeit“). Constitution of a work group for tumor cytogenetics at the University of Bremen**
1987	**Appointment as senior scientific councilor (“wissenschaftlicher Oberrat“)**
1988	**Initiation of the state doctorate / habilitation at the faculty of Biology/Chemistry of the University of Bremen**
1989	**Grant of the „*Venia legendi“ in human genetics*, supervisors: Prof. Dr. C. Fonatsch, Prof. Dr. K. Sperling, Prof. Dr. W. Schloot**
1990	**Offer for a professorship (C3) for tumor genetics and cell biology & head position of the clinical research group „Immuno-dysregulation and malignant lymphomas“ at the University of Cologne.**
1992	**Declined the offer, appointment as “Akademischer Direktor“ at the University of Bremen. Grant of the academic title "Professor"**

1993	**Bremen Cancer Award of the regional association Bremen of the German Cancer Society**
1990-1994	**Several research periods at the Center for Human Genetics (CME, Director: Prof. Dr. H. Van den Berghe) of the University of Leuven, Belgium**
1995	**Offer for being a visiting professor at the University of Leuven, Belgium**
2000	**Appointment as head of the Center for Human Genetics at the University of Bremen**
2007	**Appointment as “Leitender Akademischen Direktor „ at the University of Bremen**
February 2008	**Accepted the offer for a professorship (W2) at the research cluster of excellence “REBIRTH“ at the University of Veterinary Medicine, Hanover (50% part time)**

Memberships
German Society of Human Genetics (GfH), Association of Medical Geneticists

Current occupational activity
Head of the Center for Human Genetics, University of Bremen
Professorship (W2) within the research cluster of excellence “REBIRTH“
Academic teaching in the fields of human genetics and general genetics

Exhibit B

Tab. 4.4.1 Results of the relative quantification of *CAT-12* in human cell lines

Cell line	Avg Ct CAT-12	Avg Ct 18S	Avg ΔCt	Standard deviation ΔCt	ΔΔCt	RQ	Margin of error RQ	
FTC-133	0	8.282	/	/	/	/	/	/
S40.2/TSV40i	0	10.927	/	/	/	/	/	/
Ad 64II	0	8.506	/	/	/	/	/	/
Myco.1Ti	0	8.279	/	/	/	/	/	/
EFM 19	24.407	8.314	16.093	0.04	-2.106	4.303	+0.319	-0.346
S277	0	8.119	/	/	/	/	/	/
HeLa	0	8.329	/	/	/	/	/	/
Colo 320 HSR	0	8.295	/	/	/	/	/	/
MCF7	26.535	8.336	18.199	0.09	0	1	+0.159	-0.189

Tab 4.5.1 Relative CAT-12 expression in different mamma carcinomas

Case No.	Type	Avg Ct CAT-12	Avg Ct 18S	Avg ΔCt	ΔΔCt	RQ	Margin of error RQ	
M4	ductal	37.153	13.886	23.268	-0.159	1.117	-0.852	+3.592
M28	ductal	0	14.034	/	/	0	/	/
M34	ductal	37.215	13.314	23.901	0.474	0.72	-0.39	+0.854
M36	ductal	0	13.582	/	/	0	/	/
M42	ductal	0	13.951	/	/	0	/	/
M44	lobar	37.486	14.058	23.427	0	1	-0.106	+0.118
M49	ductal	35.101	14.234	20.867	-2.56	5.897	-1.162	+1.447
M53	ductal	0	13.916	/	/	0	/	/
M54	ductal	0	13.591	/	/	0	/	/
M56	ductal	34.939	15.09	19.849	-3.578	11.94	-6.711	+15.324
M59	ductal	37.462	14.199	23.262	-0.165	1.121	-0.158	+0.183
M62	ductal	0	15.438	/		0	/	/
M64	lobar	0	14.129	/		0	/	/
M68	ductal	0	15.014	/	/	0	/	/
M75	ductal	0	14.591	/	/	0	/	/

Exhibit C

Tab. 4.2.1 Relative CAT-12 expression in benign and malignant neoplasias as well as hyperplasias of the thyroid

Case No.	Type	Avg Ct CAT-12	Avg Ct 18S	AvgΔCt	ΔΔCt	RQ	Standard deviation ΔC_t
T51a	Follicular adenoma	34.785	16.512	18.273	-4.095	15.489	0.124
T55	Surrounding tissue	0	11.871	/	/	/	/
T69a	Surrounding tissue	0	14.58	/	/	/	/